



SEP 18 2009

K082118

510(k) Summary

As required by 21 CFR Section 807.92(c).

Submitted by: Cepheid®
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Contact: Russel K. Enns, Ph.D.

Date of Preparation: July 31, 2009

Device:

Trade name: Xpert® HemosIL® FII & FV

Common names: Factor II and Factor V Genotyping Assay.
Xpert® HemosIL® Factor II & Factor V Assay
Xpert® HemosIL® Factor II & Factor V

Type of Test: Nucleic Acid Amplification Test, DNA, Factor II
Prothrombin G20210A and Factor V G1691A (Leiden)
qualitative, genotyping

Classification name: Factor II Prothrombin and Factor V Leiden DNA Mutation
Detection Systems

Regulation number: 864.7280

Procode: NPR

Classification: Hematology

Advisory Committee:

Predicate Devices: Roche Factor II (Prothrombin) G20210A Kit (510(k)
#k033612) and
Roche Factor V Leiden Kit (510(k) #k033607)

Device Description:

The Cepheid Xpert® HemosIL® Factor II & Factor V Assay is an automated DNA test for detecting Factor II and Factor V normal and mutant alleles directly from sodium citrate or EDTA anticoagulated whole blood specimens. Blood specimens are drawn into either sodium citrate or EDTA anticoagulant tubes. Following brief mixing of the sample, the blood sample and two single-use reagents (Reagent 1 and Reagent 2) that are provided with the assay are transferred to different, uniquely-labeled chambers of the disposable fluidic cartridge (the Xpert HemosIL Factor II & Factor V cartridge). The user initiates a test from the system user interface and places the cartridge into the GeneXpert® Dx System instrument platform, which performs hands-off real-time, multiplex polymerase chain reaction (PCR) for detection of DNA. In this platform,

sample preparation, amplification, and real-time detection are all fully-automated and completely integrated.

The GeneXpert Dx System consists of a GeneXpert instrument, personal computer, a barcode scanner and the multi-chambered fluidic cartridges that are designed to complete sample preparation and real-time PCR for detection of Factor II and Factor V normal and mutant alleles in approximately 30 minutes. Each system has 1 to 16 randomly accessible modules that are each capable of performing separate sample preparation and real-time PCR tests. Each module contains a syringe drive for dispensing fluids, an ultrasonic horn for lysing nuclei, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

The Xpert HemosIL Factor II & Factor V Assay includes reagents for the detection of Factor II and Factor V normal and mutant alleles. The primers and probes in the Xpert HemosIL Factor II & Factor V Assay determine the genotype of the Factor II gene (at position 20210) and the Factor V gene (at position 1691).

The test includes a Probe Check Control (PCC) that verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability and an instrument control verifies the instrument is performing properly. Additionally, the sample functions as its own internal control since both normal and mutant gene sequences are detected, and each person tested is expected to have one of these sequence signatures.

Device Intended Use:

The Xpert™ HemosIL® Factor II & Factor V Assay is a qualitative *in vitro* diagnostic genotyping test for the detection of Factor II and Factor V alleles from sodium citrate or EDTA anticoagulated whole blood. The assay is performed on the Cepheid GeneXpert® Dx System. This test is intended to provide results for Factor II (G20210A) and Factor V Leiden (G1691A) mutations as an aid in the diagnosis in individuals with suspected thrombophilia.

Substantial Equivalence:

The Xpert HemosIL Factor II & Factor V Assay is substantially equivalent to two predicate devices, Roche Factor II (Prothrombin) G20210A Kit (510(k) #k033612) and Roche Factor V Leiden Kit (510(k) #k033607). The Xpert HemosIL Factor II & Factor V Assay and Roche Factor II (Prothrombin) G20210A Kit and Factor V Leiden Kit determine the Factor II and Factor V genotypes through real-time PCR amplification and fluorogenic target-specific hybridization detection.

Table 5.1 shows the similarities and differences between the Xpert HemosIL Factor II & Factor V Assay and the two predicate devices. The GeneXpert Dx System, used with the Xpert HemosIL Factor II & Factor V Assay, is also used to perform the Cepheid Xpert GBS Assay, the Xpert EV Assay and the Xpert MRSA Assay. The predicate devices are performed on the Roche LightCycler® system.

In a multi-center clinical comparison study, performance of the Xpert HemosIL Factor II & Factor V Assay and the Roche Factor II and Factor V Assays were each calculated relative to the gold standard, bi-directional sequencing results, and were shown to be substantially equivalent.

Table 5.1

Similarities and Differences Between the Xpert HemosIL Factor II & Factor V Assay and the Predicate Devices

Similarities (Assay)			
	Device	Predicates	
Item	Xpert HemosIL Factor II & Factor V Assay	Roche Factor II (Prothrombin) G20210A (510(k) #k033612)	Roche Factor V Leiden Kit (510(k) #k033607)
Intended Use	Rapid detection of Factor II and Factor V alleles from sodium citrate and EDTA anticoagulated whole blood	Same except detection of Factor II only from EDTA anticoagulated blood only	Same except detection of Factor V only from EDTA anticoagulated blood only
Indication for Use	Aid in the diagnosis in individuals with suspected thrombophilia	Same	Same
Technological Detection Principles	Amplification and detection system for nucleic acids using fluorescence detection.	Same	Same

Differences (Assay)			
	Device	Predicates	
Item	Xpert HemosIL Factor II & Factor V Assay	Roche Factor II (Prothrombin) G20210A (510(k) #k033612)	Roche Factor V Leiden Kit (510(k) #k033607)
Specimen Type	Anticoagulated Whole Blood	Purified DNA from human blood samples	Purified DNA from human blood samples
Sample Preparation	Automated On-line	Performed off-line	Performed off-line
Test Cartridge	Disposable single-use, multi-chambered fluidic cartridge.	Disposable single-use PCR capillary	Disposable single-use PCR capillary

Differences (Assay)			
Item	Device	Predicates	
	Xpert HemosIL Factor II & Factor V Assay	Roche Factor II (Prothrombin) G20210A (510(k) #k033612)	Roche Factor V Leiden Kit (510(k) #k033607)
Instrument System	Cepheid GeneXpert® Dx System	Roche LightCycler	Roche LightCycler
Detection Chemistry	Paired hybridization probes using Scorpions	Paired hybridization probes using fluorescence energy transfer (FRET)	Paired hybridization probes using fluorescence energy transfer (FRET)
Fluidics/Sample Preparation	Self-contained and automated after two single-dose reagent additions.	Manual	Manual
Probes	Scorpion Probes	HybProbe	HybProbe
Controls	Internal Probe check control (PCC).	External positive and negative controls required per run	External positive and negative controls required per run
Rapid test results	Approximately 30 minutes to results.	< 1 hour (not including sample prep & set-up time)	< 1 hour (not including sample prep & set-up time)
Users	Operators with no clinical lab experience to experienced clinical laboratory technologists.	CLIA High Complexity Laboratory Users	CLIA High Complexity Laboratory Users

Non-Clinical Studies:

Analytical Sensitivity

Studies were performed to determine the minimum and maximum amount of input patient specimen for both EDTA and sodium citrate anticoagulated whole blood, needed to obtain a correct genotype, such that the lower bound of the 95% confidence interval for the estimated "correct call" fraction is greater than 95%.

EDTA and sodium citrate anticoagulated blood samples were tested (n=20) at 8 volumes varying from 5 μ L to 250 μ L.

Although the assay can tolerate varying volumes from 15 μ L - 100 μ L, 50 μ L is the recommended sample volume to minimize the risk of errors associated with limited and excess sample.

Analytical Specificity

To evaluate the analytical specificity of the Xpert HemosIL Factor II & Factor V Assay, normal gene sequences containing silent single nucleotide polymorphisms (SNPs) in the probe binding region as well as outside the probe binding region were synthesized. The presence of the additional SNP in the probe binding region, in most cases, resulted in an invalid result. When a valid result was obtained, it gave the correct genotype.

The presence of an additional SNP outside the probe binding region resulted in the correct genotyping call.

Interfering Substances

Patients on heparin therapy and blood transfusion patients may have blood specimens that potentially interfere with the PCR results and lead to invalid or erroneous results.

Studies of potentially interfering substances showed no inhibition from up to 14.3 USP units/mL heparin, 16 mg/dL bilirubin, 250 mg/dL added cholesterol, or 1932 mg/dL total triglycerides (lipids). No inhibition was observed using whole blood samples which had gone through one freeze-thaw cycle (hemolyzed blood). No statistical significance was observed between matched specimens drawn into EDTA or sodium citrate.

Clinical Studies

Clinical Comparison Study

Performance characteristics of the Xpert HemosIL Factor II & Factor V Assay were determined in a multi-site investigational study at seven U.S. institutions by the Xpert HemosIL Factor II & Factor V Assay relative to bi-directional sequencing.

Specimens included those whose routine care called for collection of whole blood for Factor II and/or Factor V testing. Samples were first tested by routine methods used in each participating laboratory and then aliquots collected for study testing by Xpert HemosIL Factor II & Factor V Assay on the GeneXpert. Excess DNA was sent to a contract laboratory for bi-directional sequencing.

Performance of the Xpert HemosIL Factor II & Factor V Assay was calculated relative to bi-directional sequencing results.

Overall Results

Xpert HemosIL Factor II & Factor V Assay

A total of 1018 samples were tested for Factor II by both the Xpert HemosIL Factor II & Factor V Assay and bi-directional sequencing. A total of 1014 samples were tested for Factor V by both the Xpert HemosIL Factor II & Factor V Assay and bi-directional sequencing. To supplement the homozygous sample size, six human genomic DNA samples homozygous for Factor II and five homozygous for Factor V were also tested by the Xpert HemosIL Factor II & Factor V Assay and bi-directional sequencing. The results are presented in Table 5.2.

The Xpert HemosIL Factor II & Factor V Assay demonstrated a 99.3% overall accuracy relative to bi-directional sequencing for both Factor II and Factor V.

Table 5.2 - Xpert HemosIL Performance vs. Bi-directional Sequencing

Genotype	Number Tested	Number of Correct Calls on First Run	Number of Invalid ^a Calls on First Run	Agreement on First Run	Number of Correct Calls Including Repeat Run	Number of Invalid ^a Calls on Repeat Run	Agreement After Repeat Run
Factor II G20210A							
WT	968	927	41	95.8%	963	5	99.5%
HET	50	48	2	96.0%	48	2	96.0%
HOM	7	7	0	100.0%	7	0	100%
Overall	1025 ^b	982	43	95.8%	1018	7	99.3%
Factor V G1691A							
WT	895	860	35	96.1%	889	6	99.3%
HET	114	108	6	94.7%	113	1	99.1%
HOM	12	11	1	91.7%	12	0	100.0%
Overall	1021 ^c	979	42	95.9%	1014	7	99.3%

^aNo discordant results. Invalid results refer to "indeterminate" results.

^bBi-directional sequencing results for Factor II were not available for 4 specimens.

^cBi-directional sequencing results for Factor V were not available for 8 specimens.

Reproducibility Study

A panel of 5 specimens, consisting of one of each specimen type listed below were tested in duplicate by two different operators on 5 different days at each of three sites (3 specimens x 2 times/day x 2 operators per site x 5 days x 3 sites). One lot of Xpert HemosIL Factor II & Factor V Assay kit was used at each of the 3 testing sites. Xpert HemosIL Factor II & Factor V assays were performed according to the Xpert HemosIL Factor II & Factor V procedure. Results are summarized in Tables 5.3 – 5.6.

Study panel:

1. a sample with normal (wildtype) alleles for both Factor II & Factor V;
2. a sample heterozygous for Factor II mutation (*i.e.*, one mutant and one wildtype allele for Factor II gene) and with normal (wildtype) alleles for Factor V;
3. a sample homozygous for Factor II mutation (*i.e.*, two mutant alleles for Factor II gene) and with normal (wildtype) alleles for Factor V;
4. a sample with normal (wildtype) alleles for Factor II and homozygous for Factor V mutation (*i.e.*, two mutant alleles for Factor V gene);
5. a sample with normal (wildtype) alleles for Factor II and heterozygous for Factor V mutation (*i.e.*, one mutant and one wildtype allele for Factor V gene)..

Table 5.3 – Summary of Reproducibility Results by Site – Factor II

Specimen ID	Site 1	Site 2	Site 3	% Total Agreement by Sample
NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II HET/Factor V NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II HOM/Factor V NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II NOR/Factor V HOM	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II NOR/Factor V HET	100% (20/20)	100% (20/20)	95.0% (19/20) ^a	98.3% (59/60) ^a
% Total Agreement by Site	100% (60/60)	100% (60/60)	98.3% (59/60) ^a	99.7% (299/300) ^a

^aNo discordant results. One sample was indeterminate after retest.

Table 5.4 – Summary of Reproducibility Results by Site – Factor V

Specimen ID	Site 1	Site 2	Site 3	% Total Agreement by Sample
NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II HET/Factor V NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II HOM/Factor V NOR	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II NOR/Factor V HOM	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
Factor II NOR/Factor V HET	100% (20/20)	100% (20/20)	95.0% (19/20) ^a	98.3% (59/60) ^a
% Total Agreement by Site	100% (60/60)	100% (60/60)	98.3% (59/60) ^a	99.7% (299/300) ^a

^aNo discordant results. One sample was indeterminate after retest.

Table 5.5 – Summary of Reproducibility Results by Operator – Factor II

Specimen ID	Site 1		Site 2		Site 3		% Total Agreement by Sample
	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2	
NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II HET/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II HOM/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II NOR/Factor V HOM	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II NOR/Factor V HET	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	90.0% (9/10) ^a	98.3% (59/60) ^a
% Total Agreement by Operator	100% (50/50)	100% (50/50)	100% (50/50)	100% (50/50)	100% (50/50)	98.0% (49/50) ^a	99.7% (299/300) ^a

^aNo discordant results. One sample was indeterminate after retest.

Table 5.6 – Summary of Reproducibility Results by Operator – Factor V

Specimen ID	Site 1		Site 2		Site 3		% Total Agreement by Sample
	Op 1	Op 2	Op 1	Op 2	Op 1	Op 2	
NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II HET/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II HOM/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II NOR/Factor V HOM	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (60/60)
Factor II NOR/Factor V HET	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	100% (10/10)	90.0% (9/10) ^a	98.3% (59/60) ^a
% Total Agreement by Operator	100% (50/50)	100% (50/50)	100% (50/50)	100% (50/50)	100% (50/50)	98.0% (49/50) ^a	99.7% (299/300) ^a

^aNo discordant results. One sample was indeterminate after retest.

To assess the between lot reproducibility, the 5-specimen panel described above was analyzed two times per day over 5 testing days using each of three assay lots, at a single testing site (5 specimens x 2 runs per day x 3 lots x 5 days). A summary of the results by lot is shown in Table 5.7 & 5.8.

Table 5.7 – Summary of Reproducibility Results by Lot – Factor II

Specimen ID	Lot 1	Lot 2	Lot 3	% Total Agreement by Sample
NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II HET/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II HOM/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II NOR/Factor V HOM	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II NOR/Factor V HET	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
% Total Agreement by Lot	100% (50/50)	100% (50/50)	100% (50/50)	100% (150/150)

Table 5.8 – Summary of Reproducibility Results by Lot – Factor V

Specimen ID	Lot 1	Lot 2	Lot 3	% Total Agreement by Sample
NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II HET/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II HOM/Factor V NOR	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II NOR/Factor V HOM	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
Factor II NOR/Factor V HET	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)
% Total Agreement by Lot	100% (50/50)	100% (50/50)	100% (50/50)	100% (150/150)

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the Xpert HemosIL Factor II & Factor V Assay is substantially equivalent to the gold standard (bi-directional sequencing) and the predicate devices.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

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Senior Vice President
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904 Caribbean Drive
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SEP 1 8 2009

Re: k082118

Trade/Device Name: Xpert[®] HemosIL[®] Factor II & Factor V Assay
Regulation Number: 21 CFR 864.7280
Regulation Name: Factor V Leiden DNA mutation detection system
Regulatory Class: Class II
Product Code: NPQ, NPR, OOI
Dated: August 6, 2009
Received: August 7, 2009

Dear Dr. Enns:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

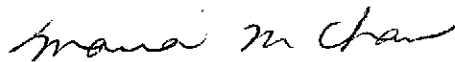
Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket

notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address <http://www.fda.gov/cdrh/industry/support/index.html>.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Maria M. Chan".

Maria M. Chan, PhD
Director
Division of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

4.0 Indications for Use Statement

510(k) Number (if known): K082118

Device Name: Xpert™ HemosIL® Factor II & Factor V Assay

Indications for Use:

The Xpert™ HemosIL® Factor II & Factor V Assay is a qualitative in vitro diagnostic genotyping test for the rapid detection of Factor II and Factor V alleles from sodium citrate or EDTA anticoagulated whole blood. The test is performed on the Cepheid GeneXpert® Dx System. This test is intended to provide rapid results for Factor II (G20210A) and Factor V (Leiden) mutations as an aid in the diagnosis in individuals with suspected thrombophilia.

Prescription Use X
(Part 21 CFR 801 Subpart D)

AND/OR Over-The-Counter Use
(21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE
OF NEEDED)


Division Sign-Off

Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K082118